

Claims 1-27, 34, and 49-52 are directed to the elected Group I invention. Among them, claims 7 and 9-11 are directed to non-elected species, and are withdrawn from further consideration.

Applicants note that at least claim 6 is a generic claim encompassing all elected and non-elected species. Claims 7-11 are dependent claims of claim 6 including all limitations of the generic claim 6. Pursuant to MPEP 809.04, "[i]f a linking claim is allowed, the examiner must thereafter examine species if the linking claim is generic thereto, or he or she must examine the claims to the non-elected inventions that are linked to the elected invention by such allowed linking claim." Thus, restrictions imposed on species encompassed by generic claims must be withdrawn upon indication of an allowable generic claim (MPEP 809). In other words, upon the allowance of a generic claim, Applicants are entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141 (MPEP 809.02(a)).

Applicants note that although the Office Action states that "claims 1-52 and 54-62" are pending, Applicants believe only claims 1-52 should be pending. Applicants also note that the Office Action states that "claims 7, 9-11, 28-33, and 35-53 are withdrawn from consideration," while it appears that only "claims 7, 9-11, 28-33, and 35-48" should be withdrawn from consideration. Furthermore, Applicants also note that the Office Action states that "claim 52 is canceled," while Applicants submit that only claim 53 is canceled. In addition, Applicants are unaware of any new claims 54-62 on file. If Applicants' understandings are incorrect, Applicants request that the Examiner point out the source of this apparent discrepancy.

Applicants also respectfully point out that the Office Action mistakenly states that Applicants traversed the Restriction Requirement on the ground that "the inventions are not independent and distinct," where no such ground of traversal was mentioned in Applicants reply dated Jan. 8, 2002 (Paper No. 7). In fact, Applicants' ground of traversal was that all Groups are related so that a search related to one Group would necessarily encompass the subject matter of other Groups, and that searching all Groups simultaneously would not impose a serious burden on the Examiner.

Applicants note that the IDS has been considered by the Examiner.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Claim objections

The Office Action asserts that the numbering of new claims is not in accordance with 37 CFR 1.126. Applicants submit that this appears to be a mistake since no new claims were added in Applicants' reply (Paper No. 7) to the Restriction Requirement or at any other time after filing the application. Reconsideration and withdrawal of this objection is respectfully requested.

The Office Action also objects to claims 49 and 51 because "albumin" is misspelled in these two claims. Accordingly, Applicants have amended claims 49 and 51 to correct this typographical error. Applicants submit that there is no narrowing of scope in any respect due to this amendment. Reconsideration and withdrawal of this objection is respectfully requested.

The Office Action also objects to the specification as containing amino acid sequences without sequence identifiers. Accordingly, Applicants have amended the specification to include proper sequence identifiers, thereby obviating this objection. Applicants have also submitted a sequence listing under 37 CFR 1.821-1.825. Reconsideration and withdrawal of this objection is respectfully requested.

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fixed

Claim rejections under 35 U.S.C. 112, second paragraph

Claim 50 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite by reciting the phrase "Cys 53 – Cys 62 ...," because there is no frame of reference in the claim or the specification supplied that will uniquely identify the amino acids of position 53-62 of the cysteine loop. Applicants respectfully disagree.

The second paragraph of page 37 indicates that Figure 1 illustrates the 3-D space-filling model of human serum albumin. Figures 4A-I illustrate the position (on the 3-D model) of the claimed cysteine loop regions of mouse serum albumin. In addition, Figure 5 unequivocally illustrates the sequence of the mouse serum albumin around the Cys53-Cys62 loop, with Cys53 and Cys62 marked in bold. As the protein sequences of the highly conserved human and mouse serum albumin were well-known in the art before the filing of the instant application (see below),

a skilled artisan would readily understand that Cys53-Cys62 stands for the cysteine loop on serum albumin starting from residue Cys53 to residue Cys62. To further support this argument, Applicants hereby submit **Exhibit A**, which shows the GenBank entry for the human (Accession No. CAA23753, first associated reference published in 1982, GenBank record last modified on Sept. 12, 1993) and mouse (CAA09617, first associated reference published in 1999, Gen Bank record last modified on Feb. 2, 2000) serum albumin precursor protein sequences. The first 24 amino acids of the precursors are removed by protease digestion after the Arg-Arg ("R-R") tryptic cleavage site, as part of the post-translational modification of serum albumins. Thus, in the mature serum albumins (both in human and mouse serum albumins), residues 53, 62, 75, 91, 90, 101, 245, 253, 266, 279, 360, 369, 461, 477, 476, 487, 558, and 567 are all cysteines. Therefore, Applicants submit that the well-known structures of the mature human and mouse serum albumins and the disclosure of the instant application unequivocally provide unique identification for amino acid positions recited in the claims. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim rejections under 35 U.S.C. 112, first paragraph

Claims 1-6, 8, 12-27, 34, and 49-52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, the Office Action alleges that the specification does not include what biological activity the heterologous polypeptide must possess. Thus, the Office Action concludes that a skilled artisan would not know how to make and use the invention because one would not know how to assay and select for the polypeptide since the biological activity of the heterologous peptide has not been defined.

Applicants submit that the Office Action seem to have misinterpreted the claimed invention, which is partly directed to the discovery that serum albumin can serve as a "protein carrier" to a heterologous polypeptide inserted herein, and confers the inserted heterologous polypeptide an increased lifetime (half-life), and thus increased observed biological activity relative to the uninserted heterologous polypeptide (for example, see paragraph bridging pages 5

and 6). Furthermore, pages 37-41 provide several examples, at least one of which demonstrates that insertion of EC (endothelial cell) binding peptides into mouse serum albumin results in an approximate 1000-fold increase in their biological inhibitory activity when compared to the uninserted control (page 41, 1st paragraph).

Applicants wish to clarify that the essence of the invention lies not in the peptide that is inserted, but in its fusion with serum albumin. Any peptide sequence which is disclosed in the published literature to have activity, such as the RGD sequence exemplified in the application, can be inserted to arrive at the claimed invention. The examples of the instant specification demonstrate that cysteine loops of serum albumin provide an effective "expression cassette" which allows the expression of such "active heterologous peptides" with increased stability, and retained/increased potency (see above). In fact, the Patent Office routinely allows claims to expression vectors comprising a specific promoter and a heterologous coding sequence without limitation as to the nature of the coding sequence or the peptide it encodes, and the instant claims are conceptually analogous to that situation.

The "40% identity" recited in the specification indicates that the "heterologous peptide" is largely or entirely unrelated to serum albumin. There could be many different types of biologically active heterologous peptides, any of which may be inserted into serum albumin according to the claimed invention. These biologically active heterologous peptides may or may not be related to one another, and they may have a wide range of biological activities, depending on the identity of each specific heterologous peptide. Since each given peptide may possess more than one biological activity (such as the ability to bind one or more other molecules, and the ability of being able to catalyze certain enzymatic reactions, etc.), the biological activity in question may also depend on the specific activity being assayed for. For example, as the specification exemplifies, the heterologous peptide can be an epitope such as the myc epitope, which possesses the biological activity of being able to bind an anti-myc antibody; the heterologous peptide can be a peptide that binds an unspecified target on endothelial cells and inhibits their growth / proliferation (EC binding peptides); or the heterologous peptide can also be a peptide that can bind a known receptor, such as the $\alpha v \beta 3$ integrin receptor, on endothelial cells and inhibit their growth / proliferation (RGD peptide). Thus, contrary to the Office Action's suggestion, there is no specific requirement for any particular biological activity, as long as the

heterologous peptide possesses at least one biological activity. In addition, contrary to the Office Action's suggestion, the heterologous peptides may or may not be related to one another, and they do not need to perform the same biological function.

Similarly, it is neither possible nor necessary to specify which regions of amino acid sequences are responsible for biological activity. The claimed invention can be used for virtually any kind of heterologous peptide with any demonstrated biological activity. Thus, it would be impractical if not impossible for Applicants to list each and every biological activity for each and every potentially useful heterologous peptide. On the other hand, a skilled artisan would not need any such information to practice the claimed invention. In view of the specification, a skilled artisan will appreciate that by inserting a biologically active (functional) peptide or a domain / region thereof into serum albumin, the lifetime of this peptide will be extended when compared to an identical but uninserted peptide or domain. The skilled artisan would already know the biological activity / function of the heterologous peptide, and the skilled artisan would also know how to assay for that particular biological function. If a region or domain of a peptide is to be inserted, the skilled artisan would know which region / domain of the full-length peptide would possess at least part of the desired biological activity of the intact peptide. In other words, the skilled artisan who wishes to practice the present invention has already identified his or her desired heterologous peptide and biological activity, and needs only to follow the specification in order to prepare the chimeric peptides of the invention and obtain the benefits taught by the inventors, including extended half-life of the biologically active peptide. Thus, the instant specification need not teach what specific biological activity an inserted heterologous peptide possesses, or how to delineate the functional domain of that heterologous peptide which still largely preserves the biological activity of the intact peptide. In fact, the claimed invention does not even recite the requirement of using partial heterologous peptides. Thus, the allegations of the Office Action that "it would be an undue burden to one of ordinary skill in the art to assay for claimed sequences," and that "it cannot be predicted from the disclosure as to which polypeptides and fragments should be isolated" are unfounded.

The claimed invention is analogous to yeast two-hybrid technology and phage display technology, wherein virtually all kinds of heterologous peptides can be inserted into a yeast two-hybrid vector or a phage display vector (see below). A skilled artisan would not require extensive

description of all possible peptides and functions that can be employed as the heterologous peptide to practice the yeast two-hybrid or the phage display technology.

Notwithstanding the fact that assays for isolation of active heterologous peptide are not required to enable the claimed invention, Applicants have described in detail many such assays on pages 22-25. Specifically, the last paragraph of page 22 refers to U.S.S.N. 09/174,943, filed on October 19, 1998, as containing methods for isolating biologically active peptides. The following pages provide further detailed description as to how such assays can be carried out to obtain suitable active peptides (pages 23-25), for example, peptides with antiproliferative, angiogenic, anti-angiogenic, or anti-infective activities on certain cells.

The Office Action also asserts that protein chemistry is probably one of the most unpredictable areas of biotechnology, and cited several examples to show that even small mutations within certain protein sequences may lead to potentially inactivating mutations that dramatically affect the biological activity and characteristic of a protein. In addition, the Office Action asserts that the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed.

Applicants submit that the Office Action confuses the effects of insertion on the function of a protein (serum albumin) that is host to another protein (heterologous peptide), with the effects of insertion on the inserted protein (heterologous peptide). Even if it is true that effects of a random mutation, even a small deletion or substitution, on the biological function of a specific protein are hard to predict, it does not necessarily follow that the function of an active sequence (heterologous peptide) will be dramatically changed when it is inserted into another protein. In fact, most properly folded proteins or domains maintain their native structure in a fusion protein. For example, the widely used yeast two-hybrid technology depends on the fusion of a DNA binding domain or a transcriptional activation domain to a protein *library* encoded by a cDNA library. If most proteins dramatically changed their function / property in fusion proteins, the yeast two-hybrid library would not be expected to encode many useful proteins, and the yeast two-hybrid technology would not have been nearly as successful as it is today. Another example is phage display, wherein a heterologous peptide or protein is expressed as a fusion protein with

a coat protein of bacteriophage, resulting in display of the heterologous peptide on the exterior surface of the virion. In both of these cases, libraries of peptides and proteins can be expressed as fusions, and the apparent success of these technologies provide further proof to the notion that most intact proteins and their functional domains remain functional in fusion proteins. OK

On the other hand, although it is possible that random insertions may cause structural problems in proteins inserted by other proteins, this is not likely to be the case in the particular case of serum albumin, especially when the insertions and/or substitutions occur at certain cysteine loop regions. According to the specification, the structure including the 3-D structure of serum albumin is well-studied (see the paragraph bridging pages 6-7). Particularly, the specification contemplates that cysteine-constrained loops may be selected for replacement, on the presumption that structural changes to the loop are unlikely to significantly affect the tertiary structure of the protein as a whole. The fact that several peptides (including the myc epitope, the RGD peptide, several EC binding peptides) have maintained or greatly enhanced their biological activities when inserted into certain serum albumin Cys loops as described in the specification further substantiates this presumption, and the Examiner has not provided evidence that refutes Applicants' experimental data.

Based on the above argument, Applicants submit that the specification has provided ample working examples that reasonably correlate with the full scope of the claimed invention, and that a skilled artisan would be able to practice the claimed invention without undue experimentation. Thus, the enablement requirement of 35 U.S.C. 112, first paragraph is met. OK
Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1-6, 8, 12-27, 34, and 49-52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the invention(s), at the time the application was filed, had possession of the claimed invention.

Specifically, the Office Action alleges that "the specification does not disclose any objective evidence regarding disclose the isolation of and assaying of the claimed polypeptides, the successful binding of a heterologous polypeptide to a tyrosine kinase receptor, the induction of apoptosis, modulation of cell proliferation or differentiation of cell types." Furthermore, the

Office Action asserts that there are no other disclosed examples that convey to a skilled artisan that Applicants were in possession of a heterologous peptide, and that there is no actual reduction to practice, sufficient descriptive information including definitive structural features critical to polypeptide activity, or complete detailed description of the function of claimed invention indicating that the claimed polypeptide was indeed isolated, produced, and assayed for the uses disclosed. Applicants respectfully disagree.

Applicants respectfully remind the Examiner that the final guidelines for 35 U.S.C. 112 clearly state that there is a strong presumption that the specification as filed provides adequate written description support for the claimed invention. Pursuant to MPEP 2163.02 (8th edition released in August, 2001) “An objective standard for determining compliance with the written description requirement is, ‘does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.’... Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed.... An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention.... Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was ‘ready for patenting’ such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete.” (emphasis added). MPEP 2163.03 also states that “rejection of an original claim for lack of written description should be rare.” A disclosure as filed is *prima facie* adequate. To support a rejection, the PTO has the burden of showing why Applicants’ evidence is insufficient. In any case where lack of written description is found, the PTO should cite documentary evidence in support of the finding.

In view of the guidelines recited above, and the arguments presented below, Applicants respectfully submit that the Office Action has failed to fully consider the factual evidence submitted by Applicants in light of the strong presumption due to the disputed terms – all of which were included in the original claims as filed – and has not shown why Applicants’ supporting evidence is insufficient. Neither does the Office Action provide documentary

evidence or convincing technical reasoning as required by the Guidelines (MPEP 2163.02) to rebut the presumption in favor of the Applicants.

Particularly, Applicants submit that Applicants have shown possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Specifically, pages 2-5 of the specification as well as the original claims 1-27, 34, 49-52 describe in detail the structure of various forms of the claimed chimeric serum albumin (SA) polypeptides. For example, the 1st full paragraph of page 2 reads:

One aspect of the present invention provides a chimeric polypeptide comprising a biologically active heterologous peptide fragment inserted into a serum albumin protein or a homolog thereof. The heterologous peptide fragment may optionally replace a portion of the serum albumin protein sequence. A peptide fragment which replaces a portion of the serum albumin protein sequence need not be of the same length as the fragment it replaces. A chimeric polypeptide according to this aspect may include more than one heterologous peptide fragment which replaces a portion of the serum albumin protein sequence. The included fragments may be identical, may be distinct sequences from a protein unrelated to serum albumin protein, or may be distinct sequences of unrelated origin.

The remaining paragraphs of the same section summarize the structures of the various claimed chimeric polypeptides, and the characteristics (length, half-life, ability to bind to various receptors, etc.) of the heterologous peptides inserted therein. Page 37 (see above) further describes the identity of various SA Cys loops into which a heterologous peptide can be inserted.

Furthermore, contrary to what the Office Action alleges, Applicants have demonstrated possession of the claimed invention by describing examples of actual reduction to practice. The example section set forth several specific examples as to how the claimed chimeric peptides can be made and used. Specifically, the example shows that various heterologous peptides (myc epitope, RGD peptide, and several EC binding peptides) have retained or greatly increased their biological activities when inserted into SA. The results are illustrated by Figures 3 and 6-8.

The Office Action alleges that the specification does not disclose the isolation of a heterologous peptide, or assay methods to measure biological activity. Applicants submit that it is the chimeric SA polypeptide that is claimed, not the isolation of a heterologous peptide nor assaying of the biological function of the peptide. These entities and techniques were well known

in the art, and thus need not be described in detail in the specification; one of skill in the art would readily envision the full scope of these terms without the need for voluminous explication. Thus, to meet the written description requirement, the specification does not need to describe either the isolation of a heterologous peptide, or to provide a way of assaying the biological function of the claimed polypeptide.

The Office Action also alleges that there is no evidence that the chimeric polypeptide exhibits a half-life of no less than 14 or 10 days in the blood. According to the written description guideline recited above, to support a written description rejection, the PTO has the burden of showing why Applicants' evidence is insufficient. In any case where lack of written description is found, the PTO should cite documentary evidence in support of the finding.

Applicants submit that page 3, third paragraph of the specification describes that "the chimeric polypeptide has a half-life in the blood no less than 10 days, preferably no less than about 14 days, and most preferably no less than 50% of the half-life of the native serum albumin protein or homolog thereof." Also in the paragraph bridging pages 5-6, the specification teaches that "SA is the major protein constituent of the circulatory system, has a half-life in the blood of about three weeks (Rothschild, M.A. et al. *Hepatology* **1988**, 8, 385-401)," and that "[f]usion proteins wherein a therapeutic polypeptide has been covalently linked to serum albumin have been shown to have serum half-lives many times longer than the half-life of the therapeutic peptide itself (Syed, S. et al. *Blood* **1997**, 89, 3243-3252; Yeh, P. et al. *Proc. Natl. Acad. Sci. USA* **1992**, 89, 1904-1908). In both cited publications, the half-life of the fusion protein was more than 140 times greater than that of the therapeutic polypeptide itself, and approached the half-life of unfused serum albumin." Thus, there is strong evidence supporting the Applicants' assertion that the claimed SA chimeric polypeptides have a half-life approaching that of unfused SA – namely no less than 10-14 days or 50% of the 3-week natural half-life of SA. On the contrary, the Office Action has failed to provide either documentary evidence or convincing technical reasoning as required by the Guidelines (MPEP 2163.02) to rebut the presumption in favor of the Applicants.

Applicants respectfully remind the Examiner that the Supreme Court recently articulated a standard whereby the PTO must establish a rational connection between the agency's fact-

findings and its ultimate action. *Dickinson v. Zurko*, 119 S.Ct. 1816 (1999). In light of Applicants' arguments of record, and the presumption in favor of Applicants, it is respectfully asserted that the present rejection is not supported by substantial evidence, and as such, fails to rise above the "arbitrary, capricious" standard applied under the "substantial evidence" test of Section 706(2)(E) of the Administrative Procedure Act. The Office Action has not cited any relevant art nor relied on any other fact-finding results to rebut the presumption in favor of Applicants.

Similarly, the same argument applies to the Office Action's allegations that the Applicants have not disclosed any objective evidence regarding the successful binding of a heterologous polypeptide to a tyrosine kinase receptor, the induction of apoptosis, modulation of cell proliferation or differentiation of cell types. In fact, the specification provides detailed description of various types of receptors to which a heterologous peptide may bind. The example section also provides a working example of MSA-RGD chimeric peptide which binds to the integrin receptor $\alpha v \beta 3$. A skilled artisan will readily appreciate that any usual ligands of a receptor tyrosine kinase (such as EGF for EGF receptor, PDGF for PDGF receptor, etc.) can be the "heterologous peptide" inserted into SA. As to apoptosis, the example shows that MSA-RGD fusion can induce apoptosis in tumor cell line NCI-1869 (page 41 and Figure 8). Regarding modulation of cell proliferation and differentiation, the specification on page 4, 2nd paragraph, reads: "a peptide fragment that inhibits angiogenesis and which may be incorporated into a subject polypeptide is RGD (Arg-Gly-Asp), or a sequence which includes the sequence RGD (e.g., VRGDF). *Analogous methods may be used to modulate conditions such as cell proliferation, cell differentiation, and cell death.*" (emphasis added). The example also demonstrates that several EC binding peptides can efficiently inhibit endothelial cell proliferation, at a rate that is about 1000-fold more efficient than the uninserted peptide control (page 41, 1st paragraph). Again, the Office Action has failed to provide any documentary evidence or convincing technical reasoning as required by the Guidelines (MPEP 2163.02) to rebut the presumption in favor of the Applicants.

For the reasons presented above, Applicants submit that the specification has provided not only detailed description of the claimed invention, but also numerous working examples (actual reduction to practice). Thus, all pending claims as amended fully comply with the written

description requirement. Accordingly, reconsideration and withdrawal of rejection under 35 U.S.C. 112, first paragraph is respectfully requested.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945**. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

Respectfully Submitted,

Date: July 2, 2002

Customer No: 28120

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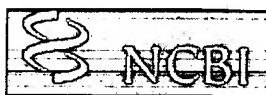
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 ☐ Structure
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 REFERENCE 1 (residues 1 to 608)
 AUTHORS Cable, J., Harris, P.D., Tinsley, R.C. and Lazarus, C.M.
 TITLE Phylogenetic analysis of Gyrodactylus spp. (Platyhelminthes:
 Monogenea) using rDNA sequences
 JOURNAL Can. J. Zool. 77, 1439-1449 (1999)
 REFERENCE 2 (residues 1 to 608)
 AUTHORS Van Reeth, T., Gabant, P., Dreze, P., Szpirer, J. and Szpirer, C.
 JOURNAL Unpublished
 REFERENCE 3 (residues 1 to 608)
 AUTHORS Van Reeth, T.
 TITLE Direct Submission
 JOURNAL Submitted (18-SEP-1998) Van Reeth T., Departement de Biologie
 Moleculaire, Universite Libre de Bruxelles, Laboratoire de Biologie
 du Developpement, rue des chevaux, 67, 1640 Rhode St Genese,
 BELGIUM

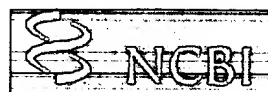
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EXHIBIT A



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 REFERENCE 1 (residues 1 to 609)
 AUTHORS Dugaiczyk, A., Law, S.W. and Dennison, O.E.
 TITLE Nucleotide sequence and the encoded amino acids of human serum
 albumin mRNA
 JOURNAL Proc. Natl. Acad. Sci. U.S.A. 79 (1), 71-75 (1982)
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 PUBMED 6275391

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Revised: October 24, 2001.

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